

--40. A recombinant polypeptide having the ability to bind to TNF which is encoded by DNA selected from the group consisting of:

A) DNA comprising the sequence:

ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT
GGA CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA GAT AGT
GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA AAT AAT TCG
ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC TTG TAC AAT
GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC AGG GAG TGT
GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC CTC AGA CAC
TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG GGT CAG GTG
GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC GTG TGT GGC
TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT GAA AAC CTT
TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT GGG ACC GTG
CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG TGC ACC TGC
CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT GTC TCC TGT
AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG TTG TGC CTA
CCC CAG ATT GAG AAT GTT AAG GGC ACT GAG GAC TCA GGC ACC
ACA GTG CTG TTG CCC CTG GTC ATT TTC TTT GGT CTT TGC CTT
TTA TCC CTC CTC TTC ATT GGT TTA ATG TAT CGC TAC CAA CGG
TGG AAG TCC AAG CTC TAC TCC ATT GTT TGT GGG AAA TCG ACA
CCT GAA AAA GAG GGG GAG CTT GAA GGA ACT ACT ACT AAG CCC
CTG GCC CCA AAC CCA AGC TTC AGT CCC ACT CCA GGC TTC ACC
CCC ACC CTG GGC TTC AGT CCC GTG CCC AGT TCC ACC TTC ACC
TCC AGC TCC ACC TAT ACC CCC GGT GAC TGT CCC AAC TTT GCG
GCT CCC CGC AGA GAG GTG GCA CCA CCC TAT CAG GGG GCT GAC
CCC ATC CTT GCG ACA GCC CTC GCC TCC GAC CCC ATC CCC AAC
CCC CTT CAG AAG TGG GAG GAC AGC GCC CAC AAG CCA CAG AGC
CTA GAC ACT GAT GAC CCC GCG ACG CTG TAC GCC GTG GTG GAG
AAC GTG CCC CCG TTG CGC TGG AAG GAA TTC GTG CGG CGC CTA
GGG CTG AGC GAC CAC GAG ATC GAT CGG CTG GAG CTG CAG AAC
GGG CGC TGC CTG CGC GAG GCG CAA TAC AGC ATG CTG GCG ACC
TGG AGG CGG CGC ACG CCG CGG CGC GAG GCC ACG CTG GAG CTG
CTG GGA CGC GTG CTC CGC GAC ATG GAC CTG CTG GGC TGC CTG
GAG GAC ATC GAG GAG GCG CTT TGC GGC CCC GCC GCC CTC CCG
CCC GCG CCC AGT CTT CTC AGA TGA

B) DNA comprising the sequence:

GAT AGT GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA
AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC
TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC
AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC
CTC AGA CAC TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG
GGT CAG GTG GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC
GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT
GAA AAC CTT TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT
GGG ACC GTG CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG
TGC ACC TGC CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT
GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG
TTG TGC CTA CCC CAG ATT GAG AAT; and

C) a fragment or variant of A or B.

41. A polypeptide according to claim 40, wherein said polypeptide is encoded by

DNA comprising the sequence:

R² GAT AGT GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA
AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC
TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC
AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC
CTC AGA CAC TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG
GGT CAG GTG GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC
GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT
GAA AAC CTT TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT
GGG ACC GTG CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG
TGC ACC TGC CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT
GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG
TTG TGC CTA CCC CAG ATT GAG AAT

wherein R² is absent or is a DNA comprising a sequence coding for a polypeptide which
can be cleaved *in vivo*, or a fragment or variant thereof.

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42. A polypeptide according to claim 41, wherein R² is a DNA comprising a sequence which codes entirely or partly for a signal sequence.

43. A polypeptide according to claim 41, wherein R² is a DNA comprising the sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA or a fragment or variant thereof.

44. A polypeptide according to claim 42, wherein R² is a DNA comprising the sequence R³ CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA, wherein R³ is a DNA coding for a signal peptide, or a fragment or variant thereof.

45. A polypeptide according to claim 44, wherein R³ is a DNA comprising the sequence:

ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT
GGA, or

or a fragment or variant thereof.

46. A recombinant polypeptide encoded by a nucleic acid which hybridizes with DNA complementary to the DNA defined in claim 40 under conditions of low stringency and said polypeptide has the ability to bind TNF.

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47. A recombinant polypeptide having the ability to bind TNF selected from the group consisting of:

A) a polypeptide comprising the amino acid sequence:

met gly leu ser thr val pro asp leu leu leu pro leu val
leu leu glu leu leu val gly ile tyr pro ser gly val ile
gly leu val pro his leu gly asp arg glu lys arg asp ser
val cys pro gln gly lys tyr ile his pro gln asn asn ser
ile cys cys thr lys cys his lys gly thr tyr leu tyr asn
asp cys pro gly pro gly gln asp thr asp cys arg glu cys
glu ser gly ser phe thr ala ser glu asn his leu arg his
cys leu ser cys ser lys cys arg lys glu met gly gln val
glu ile ser ser cys thr val asp arg asp thr val cys gly
cys arg lys asn gln tyr arg his tyr trp ser glu asn leu
phe gln cys phe asn cys ser leu cys leu asn gly thr val
his leu ser cys gln glu lys gln asn thr val cys thr cys
his ala gly phe phe leu arg glu asn glu cys val ser cys
ser asn cys lys lys ser leu glu cys thr lys leu cys leu
pro gln ile glu asn val lys gly thr glu asp ser gly thr
thr val leu leu pro leu val ile phe phe gly leu cys leu
leu ser leu leu phe ile gly leu met tyr arg tyr gln arg
trp lys ser lys leu tyr ser ile val cys gly lys ser thr
pro glu lys glu gly glu leu glu gly thr thr thr lys pro
leu ala pro asn pro ser phe ser pro pro thr pro gly phe thr
pro thr leu gly phe ser pro val pro ser ser thr phe ala
ser ser ser thr tyr thr pro gly asp cys pro asn phe
ala pro arg arg glu val ala pro pro tyr gln gly ala asp
pro ile leu ala thr ala leu ala ser asp pro ile pro asn
pro leu gln lys trp glu asp ser ala his lys pro gln ser
leu asp thr asp asp pro ala thr leu tyr ala val val glu
asn val pro pro leu arg trp lys glu phe val arg arg leu
gly leu ser asp his glu ile asp arg leu glu leu gln asn
gly arg cys leu arg glu ala gln tyr ser met leu ala thr
trp arg arg arg thr pro arg arg glu ala thr leu glu leu
leu gly arg val leu arg asp met asp leu leu gly cys leu
glu asp ile glu glu ala leu cys gly pro ala ala leu pro
pro ala pro ser leu leu arg;

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B) a polypeptide comprising the amino acid sequence:

asp	ser	val	cys	pro	gln	gly	lys	tyr	ile	his	pro	gln	asn
asn	ser	ile	cys	cys	thr	lys	cys	his	lys	gly	thr	tyr	leu
tyr	asn	asp	cys	pro	gly	pro	gly	gln	asp	thr	asp	cys	arg
glu	cys	glu	ser	gly	ser	phe	thr	ala	ser	glu	asn	his	leu
arg	his	cys	leu	ser	cys	ser	lys	cys	arg	lys	glu	met	gly
gln	val	glu	ile	ser	ser	cys	thr	val	asp	arg	asp	thr	val
cys	gly	cys	arg	lys	asn	gln	tyr	arg	his	tyr	trp		
ser	glu	asn	leu	phe	gln	cys	phe	asn	cys	ser	leu	cys	leu
asn	gly	thr	val	his	leu	ser	cys	gln	glu	lys	gln	asn	thr
val	cys	thr	cys	his	ala	gly	phe	phe	leu	arg	glu	asn	glu
cys	val	ser	cys	ser	asn	cys	lys	lys	ser	leu	glu	cys	thr
lys	leu	cys	leu	pro	gln	ile	glu	asn;	and				

C) a fragment, variant, or functional derivative of A or B.

48. A polypeptide according to claim 47, wherein said polypeptide is selected

from the group consisting of:

a polypeptide comprising the amino acid sequence:

R ₂	asp	ser	val	cys	pro	gln	gly	lys	tyr	ile	his	pro	gln	asn
	asn	ser	ile	cys	cys	thr	lys	cys	his	lys	gly	thr	tyr	leu
	tyr	asn	asp	cys	pro	gly	pro	gly	gln	asp	thr	asp	cys	arg
	glu	cys	glu	ser	gly	ser	phe	thr	ala	ser	glu	asn	his	leu
	arg	his	cys	leu	ser	cys	ser	lys	cys	arg	lys	glu	met	gly
	gln	val	glu	ile	ser	ser	cys	thr	val	asp	arg	asp	thr	val
	cys	gly	cys	arg	lys	asn	gln	tyr	arg	his	tyr	trp		
	ser	glu	asn	leu	phe	gln	cys	phe	asn	cys	ser	leu	cys	leu
	asn	gly	thr	val	his	leu	ser	cys	gln	glu	lys	gln	asn	thr
	val	cys	thr	cys	his	ala	gly	phe	phe	leu	arg	glu	asn	glu
	cys	val	ser	cys	ser	asn	cys	lys	lys	ser	leu	glu	cys	thr
	lys	leu	cys	leu	pro	gln	ile	glu	asn;					

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wherein R_2 is absent or is a polypeptide which can be cleaved *in vivo*; and
a fragment, variant, or functional derivative thereof which binds TNF.

Σ

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~~49.~~ A polypeptide according to claim ¹²~~48~~, wherein said polypeptide includes at least one additional amino acid at the amino-terminus, at the carboxyl-terminus, or at both the amino-terminus and at the carboxyl-terminus.

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~~50.~~ A polypeptide according to claim ¹⁵~~49~~, wherein said polypeptide includes at least one additional amino acid at the amino-terminus and at the carboxyl-terminus.

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~~51.~~ A polypeptide according to claim ¹⁵~~49~~, wherein said polypeptide includes at least one additional amino acid at the amino-terminus.

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~~52.~~ A polypeptide according to claim ¹⁷~~51~~, wherein said polypeptide includes a methionine at the amino-terminus.

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~~53.~~ A polypeptide according to claim ¹⁵~~49~~, wherein said polypeptide includes at least one additional amino acid at the carboxyl-terminus.

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54. A polypeptide according to claim 48, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

55. A polypeptide according to claim 40, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

56. A polypeptide according to claim 50, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

57. A polypeptide according to claim 51, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

58. A polypeptide according to claim 52, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

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59. A polypeptide according to claim 53, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

60. A polypeptide according to claim 54, wherein said polypeptide is a variant having at least one intrasequence amino acid insertion in the sequence of claim 48.

61. A polypeptide according to claim 54, wherein said polypeptide is a variant having at least one intrasequence amino acid deletion in the sequence of claim 48.

62. A polypeptide according to claim 54, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution in the sequence of claim 48.

63. A polypeptide according to claim 62, wherein said polypeptide includes a methionine at the amino-terminus.

64. A polypeptide according to claim 62, wherein said polypeptide includes a methionine at the amino-terminus and said amino acid substitution is at a glycosylation site.

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65. A polypeptide according to claim 62, wherein said amino acid substitution is at a glycosylation site.

66. A recombinant polypeptide encoded by a nucleic acid that hybridizes to a DNA complementary DNA encoding the amino acid sequence defined in claim 48 under conditions of low stringency and said polypeptide has the ability to bind TNF.

67. A pharmaceutical composition comprising a polypeptide of claim 40 and a pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising a polypeptide of claim 48 and a pharmaceutically acceptable carrier.--

REMARKS

Applicants canceled claims 19 to 21 without prejudice or disclaimer. Applicants amended claim 27 above. Applicants also added claims 40-68 above. Claims 27 to 30 were added November 18, 1996, and claims 31 to 39 were added April 29, 1997.

Claims 24 and 27 to 68 are pending.

1. Objection To Claim 2

The Examiner contended that claim 2 was improper since it included the term "optionally." Office Action at page 2, Item No. 1. The Examiner asserted that a Board